MOH/P/PAK/471.21(TR)-e

TECHNOLOGY REVIEW (MINI-HTA)

THERAPEUTIC DRUG MONITORING (TDM) FOR ANTI-TUBERCULOSIS

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
003/2021

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Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

e-ISBN:978-967-2887-18-8

SUGGESTED CITATION: Maharita AR and Izzuna MMG. Therapeutic Drug Monitoring (TDM) for Anti-Tuberculosis. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2021. 54p. Report No.: 003/2021. e-ISBN:978-967-2887-18-8

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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EXECUTIVE SUMMARY

Background

In 2018, the reported tuberculosis cases in Malaysia were 25,173 with an estimated incidence rate of 92 cases per 100,000 populations. Globally, 7.1 million people with TB were diagnosed and 1.4 million died of TB in 2019. In 2018, the United Nations set a target to diagnose and treat 40 million people with TB including 3.5 million children and 1.5 million of drug-resistant patients in a five-year period (2018-2022). Since then, the TB treatment coverage increased from 69% in 2018 to 71% in 2019.

On the other hand, drug-resistant among TB patients keep increasing. A systematic review (SR) in 2016 stated that generally, first-line treatment for drug-susceptible TB was effective but inadequate exposure to anti-TB may constitute one of the factors underlying suboptimal treatment response. This suggested that ensuring appropriate serum concentrations of anti-TB drugs in patients on treatment for active TB may improve treatment outcomes. Measurement of blood drug concentrations may also be referred as therapeutic drug monitoring.

Therapeutic drug monitoring (TDM) is an individualisation of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window. By combining knowledge of pharmaceutics, pharmacokinetics and pharmacodynamics, TDM enables the assessment of the efficacy and safety of a particular medication in a variety of clinical settings. The goal of TDM is to individualise therapeutic regimens for optimal patient benefit.

This technology review was requested by the Head of Sector of Tuberculosis and Leprosy Control, Disease Control Division, Ministry of Health based on issues raised by Respiratory Physician and Paediatric Specialist during Meeting of Tuberculosis Drug-resistant Management Meeting 1/2020.

Objective/ aim

The objective of this technology review was to assess the efficacy/effectiveness, safety and cost-effectiveness of therapeutic drug monitoring (TDM) in tuberculosis treatment.

Results and conclusions:

Search results

A total of **739** records were identified through the Ovid interface and PubMed. After removal of 635 titles, **104** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **46** relevant abstracts and the full text were retrieved. After reading, appraising and applying the inclusion and exclusion criteria, **9** were included while **37** were excluded since the studies were already included in systematic review

and meta-analysis (n=6), irrelevant study design and unrelated topics (n=20) and studies not addressing specific process (n=11). **Nine** full text articles finally selected for this review consisted of one systematic reviews, five cohort studies, and three case-control studies.

Efficacy/Effectiveness

In patients on first line anti-TB treatment, concentration level of the anti-TB drugs was not associated with patient outcome. However, for second line anti-TB drugs, TDM was used to ensure therapeutic drug level to avoid toxicity.

Safety

No evidence retrieved regarding the safety of TDM used in anti-TB drugs. However, TDM used for detection of any over dosage or low dose anti-tuberculosis among patients with sign and symptom of toxicity and unresponsive towards treatment.

Organisational

Poor compliance of anti-TB drug was reported in sputum non-conversion group compared to sputum conversion group.

Economic implication

No cost-effectiveness study retrieved related to TDM for anti-TB drug

Methods

Literature search was conducted with help from an Information *Specialist* who searched for published articles pertaining to TDM in TB treatment. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 10th August 2021. Parallel searches were run in PubMed, US FDA, CADTH, and INAHTA database. No limits were applied to the search. Any additional articles were identified from reviewing the references of retrieved articles. The last search was performed on 12th August 2021.

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ABBREVIATIONS

AEs	Adverse events or adverse effects
Anti-TB	Anti-Tuberculosis
AUC	Area Under Curve
CS	Cycloserine
DST	Drug-Susceptibility Testing
EBA	Early Bactericidal Activity
EMB	Ethambutol
HPLC	High-Performance Liquid Chromatography
INH	Isoniazid
LLOQ	Lower limit of quantification
MDR-TB	Multidrug Resistance-Tuberculosis
MDRR-TB	Multidrug Rifampicin Resistance-Tuberculosis
MIC	Minimum Inhibitory Concentration
PD	Pharmacodynamic
PK	Pharmacokinetic
PZA	Pyrazinamide
QC	Quality Control
RE	Relative Error
RMP	Rifampicin
RSD	Relative Standard Deviation
STM	Streptomycin
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
UHC	Universal Health Coverage
ULHPLC	Ultra-Light High Performance Liquid Chromatography
WHO	World Health Organisation

1.0 BACKGROUND

In 2018, the reported tuberculosis cases in Malaysia were 25,173 with an estimated incidence rate of 92 cases per 100,000 populations.[1] Globally, 7.1 million people with TB were diagnosed and 1.4 million died of TB in 2019. Of the 7.1 million, 58% were men, 34% were women and 8% were children. The World Health Organisation (WHO) reported that about 85% of TB patients can be successfully treated with six-month drug regimen. In 2018, the United Nations set a target to diagnose and treat 40 million people with TB including 3.5 million children and 1.5 million of drug-resistant patients in a five-year period (2018-2022). Since then, the TB treatment coverage increased from 69% in 2018 to 71% in 2019 and the Global TB Report 2020 updated that four WHO regions achieved treatment coverage levels above 75%; those regions were America, Europe, South-East Asia and Western Pacific.[2]

On the other hand, drug-resistant among TB patients keep increasing, for example rifampicin (RMP) resistance which increased from 51% in 2018 to 61% in 2019 globally. In addition to that, a total of 206,030 people with multidrug- or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2019, a 10% increase from 186,883 in 2018.[2] A systematic review (SR) in 2016 stated that generally, first-line treatment for drug-susceptible TB was effective but inadequate exposure to anti-TB may constitute one of the factors underlying suboptimal treatment response. This suggested that ensuring appropriate serum concentrations of anti-TB drugs in patients on treatment for active TB may improve treatment outcomes. The relationship between low drug concentrations and patient's outcome was poorly described, but some evidence suggests that below-normal drug concentrations may have potential impact on the proportion of patients with treatment failure, relapse and drug resistance.[3] Measurement and monitoring of serum/blood drug concentrations may also be referred as therapeutic drug monitoring.[4]

Therapeutic drug monitoring (TDM) is an individualisation of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window. By combining knowledge of pharmaceutics, pharmacokinetics (PK) and pharmacodynamics (PD), TDM enables the assessment of the efficacy and safety of a particular medication in a variety of clinical settings. The goal of TDM is to individualise therapeutic regimens for optimal patient benefit.[4] Although routine TDM was not universally performed in patients receiving anti-TB treatment, TDM may benefit patients with specific high-risk conditions, such as HIV, DM, malnutrition, renal and hepatic impairment or patients with disease from drug-resistant strains even in pregnancy and among children.[3] Bolhuis MS et al. reported in their review that Tuberculosis Center Beatrixoord University Medical Center Groningen, Groningen, The Netherlands routinely applied TDM for multidrug-resistant tuberculosis (MDR-TB) and achieved high success rates for treatment of MDR-TB.[5]

This technology review was requested by the Head of Sector of Tuberculosis and Leprosy Control, Disease Control Division, Ministry of Health based on issues raised by Respiratory Physician and Paediatric Specialist during Tuberculosis Drug-resistant Management Meeting 1/2020.

2.0 OBJECTIVE / AIM

The objective of this technology review was to assess the efficacy/effectiveness, safety and cost-effectiveness of therapeutic drug monitoring (TDM) in tuberculosis treatment.

3.0 TECHNICAL FEATURE

3.1 Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is a clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream especially at therapeutic level, thereby optimising individual dosage regimes.[4] The goal of TDM is to assist in maximizing the effects of treatment/drugs at optimum dose and also to avoid toxicity. The basic assumption of the TDM is that the circulating concentration of a drug correlates better with pharmacological effect than the dose of the treatment/drugs.[6]

There were various methods for TDM, as listed below.[6]

1) Chemical assays
   i. Spectrophotometry: the principle is scattering of the incoming rays of light into various components by the analytes (plasma containing drug of interest)
   ii. Chromatography: based on different retention times of the analytes in a suitably packed column when flushed with a suitable carrier or eluent (solvent)

2) Immunological assays: basically, it is made up of three components; antigen, antibody and antigen-antibody complex.
   i. Radioimmunoassay (RIA)
   ii. Enzyme immunoassay (EIA)
   iii. Fluorescence polarisation immunoassay (FPIA)

The TDM has several advantages towards anti-TB management including to ease the dosing of drugs in the blood, to ensure the correct drug dose, minimising adverse events and maximising regimen efficacy.[7] According to Clinical Practice Guideline of Ministry of Health, Malaysia, Drug sensitivity test (DST) must be done for TB patients. When the results become available, the anti-TB regimen should be adjusted appropriately.[8]

Drug-Susceptibility Testing (DST)

DST is essential to ensure that the patient is on an appropriate regimen in preventing drug resistance development. However, phenotypic DST is costly (require lab capacity), technically demanding (non-viable samples, contamination risk and interpretation which lead to delays) and time consuming (1 – 2 weeks or longer). Phenotypic DST allow Minimum Inhibitory Concentration (MIC) determination which can be combined with Area Under the Curve (AUC) TDM to determine the appropriate dose of an individual drug.[7]

4.0 METHODS

Literature search was conducted by the author and with help of an *Information Specialist* who searched for full text articles pertaining to TDM for anti-tuberculosis.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface:

- MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 10th August 2021
- PubMed
- Other websites: INAHTA, CADTH

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on humans. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 12th August 2021.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using the Critical *Appraisal Skills Programme (CASP) checklist* and graded according to the US/ *Canadian Preventive Services Task Force* (**Appendix 2**) and *ROB 2.0* assessment for RCT. Data were extracted and summarised in the evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Tuberculosis, mycobacterium tuberculosis, TB patient, anti-TB, tuberculosis drug, anti-tuberculosis
b.	**Intervention**	therapeutic drug monitoring, TDM
c.	**Comparator**	(None)
d.	**Outcomes**	Serum concentration, accuracy, precision
e.	**Study design**	Systematic review, randomised control trial, observational study and cross-sectional study
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Animal study
b.	Non-English full text articles (after abstract selection process)	

5.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 2**. A total of **739** records were identified through the Ovid interface and PubMed. After removal of 635 titles, **104** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **46** relevant abstracts and the full text were retrieved. After reading, appraising and applying the inclusion and exclusion criteria, **nine studies** were included while **37** were excluded since the studies were already included in systematic review and meta-analysis (n=6), irrelevant study design and unrelated topics (n=20) and studies not addressing specific process (n=11). **Ten** full text articles were finally selected for this review consisted of one systematic reviews,

six cohort studies, and three case-control studies. The studies were conducted mainly in United States, China, India, Denmark, and Korea.

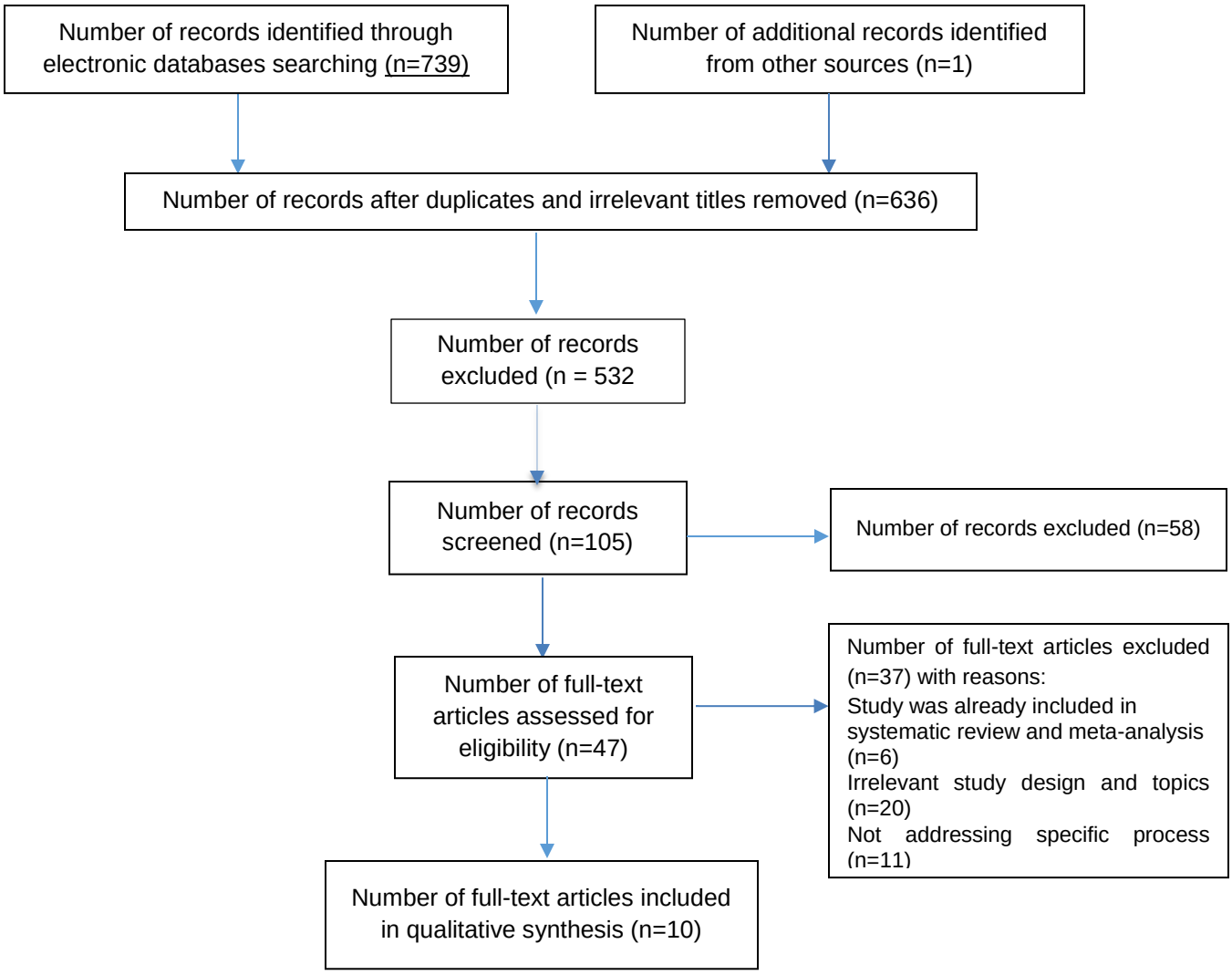

Figure 2: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

The risk of bias in the included studies were assessed using domain-based evaluation. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

Overall, the risk of bias was low for systematic review, although the included studies design varied, the main objective was related to the role of TDM in anti-tuberculosis drug. For other included studies, overall, the risk of bias was low and moderate especially in studies with small sample size (in two cohort studies). The results of risk of bias of included studies are summarised in **Figure 3.1 and 3.2**

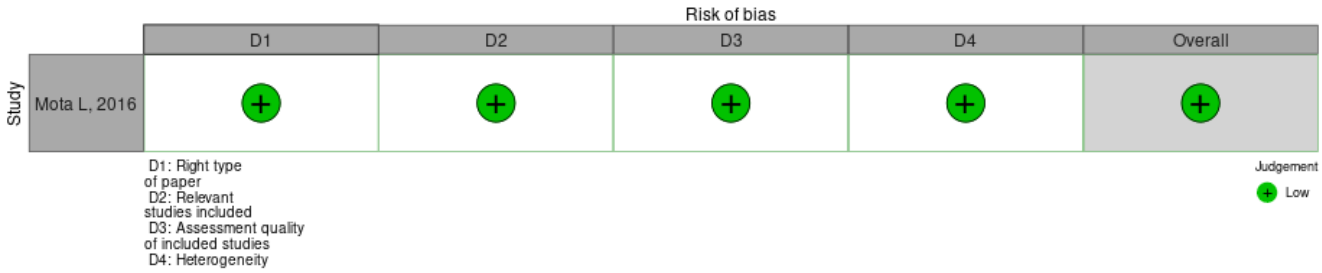

Figure 3.1: Risk of Bias of Systematic Review

Figure 3.2: Risk of Bias of Cohort Study

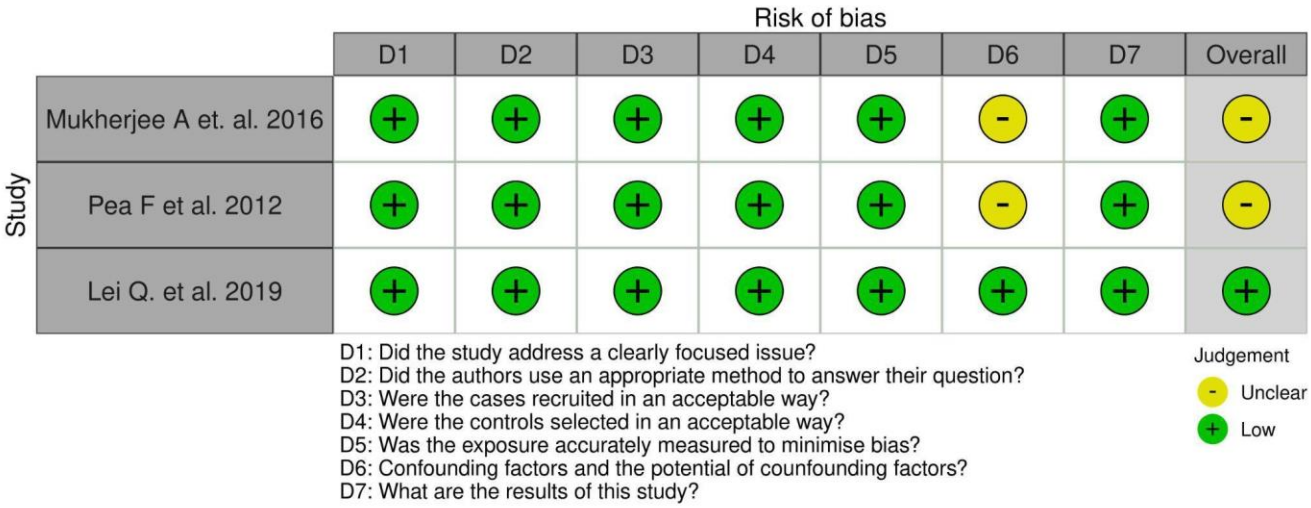

Figure 3.3: Risk of Bias of Case-Control Study

5.1 EFFICACY / EFFECTIVENESS

5.1.2 Therapeutic Drug Monitoring and Patient Outcome

Mota L. et. al. conducted SR and MA to summarise the existing literature on TDM in first-line drugs (rifampicin (RMP), isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA). The search for published literature was covered from 1970 to March 2014. The main inclusion criteria for the literature were studies of medications for the treatment of active TB, and reported the two-hour drug concentrations (C_{2h}) values on ≥1 oral first-line anti-TB medications. The C_{2h} was thought to approximate the peak serum drug concentration (C_{max}). The reported concentration for each drug varied across studies, thus the authors individually classified the low concentration level for each drug as shown in Table 1. There were 41 clinical studies included with a total of 2,727 subjects and consisted of 16 (39%) cross-sectional studies, 14 (34%) cohort's studies, 6 (15%) case controls, 3 (7%) RCTS and 2 (5%) cross-over studies. Thirteen of the studies (32%) were performed in low TB-incidence countries and 28 studies (68%) were performed in high TB-incidence countries. The studies were pooled by study quality, design, region, dosing modality and patient characteristics. The included studies also reported certain comorbidity; 20 studies (49%) examined C_{2h} in subjects with TB without comorbid HIV or DM, 11 studies (27%) involved TB- HIV co-infected populations and three studies (7%) reported on individuals with TB and DM. Table 1 showed the overall pooled proportion of subject with low C_{2h} reported in the included studies. The authors also compared the pooled proportion of subjects with low C_{2h} based on study quality; high quality studies versus low quality studies, in Table 1 and based on comorbidities in Table 2. Other findings included pooled proportion of subjects with low C_{2h} by dosing modality and other covariates which were simplified in Table 3. The authors stated that they could not identify a significant difference in the proportion of subjects with low C_{2h} using meta-regression for DM, HIV, high versus low incidence, weight (>60kg to <60kg) and dosing

modality. As for the clinical outcome in patients with low C_{2h}, 12 studies reported on TB clinical outcomes where only three studies showed association between low TB drug levels and unsuccessful treatment outcomes. Those unsuccessful outcomes were defined as longer time to culture conversion, at least one positive culture at week four, eight or 24/32 and treatment failure or death during anti-tuberculosis treatment. One study found no significant association between slow culture conversion and RMP levels after a logarithmic transformation. Eight studies found no association between low levels and treatment outcomes that were defined as relapse, treatment failure, treatment interruption, development of drug resistance or death or transfer out. With regard to cure as an outcome, only four studies provided a well-defined cure. However, the authors did not analyse the outcome separately.[3, level 1]

Table 1. Overall pooled proportion of subjects with low C_{2h} and proportion by study quality

Comorbid / First-line TB Drugs	Low level of C_{2h} (mg/L)	Overall pooled subjects with low C_{2h}		Proportion of subjects based on Study Quality	
		Proportion of subjects	Number of studies	High study quality	Low study quality
Isoniazid	< 3mg/l	0.43 (95% CI 0.32 - 0.55)	26	0.39 (95% CI 0.26-0.54)	0.49 (95% CI 0.28 – 0.71)
Rifampicin	< 8mg/l	0.67 (95% CI 0.60 - 0.74)	36	0.70 (95% CI 0.52-0.83)	0.65 (95% CI 0.57-0.72)
Ethambutol	< 2mg/l	0.27 (95% CI 0.17 - 0.38)	11	0.34 (95% CI 0.24-0.46)	0.23 (95% CI 0.11-0.41)
Pyrazinamide	< 35mg/l	0.12 (95% CI 0.07 - 0.19)	20	0.06 (95% CI 0.02-0.22)	0.15 (95% CI 0.09-0.24)

Table 2: Pooled proportion of subjects with low C_{2h} levels in TB patients with / without HIV or DM

Comorbid / First-line TB Drugs	TB with / without HIV		TB with / without DM	
	With HIV	Without HIV	With DM	Without DM
Isoniazid	0.36 (95% CI 0.19-0.57)	0.42 (95% CI 0.28-0.58)	0.89 (95% CI 0.36-0.99)	0.42 (95% CI 0.28-0.58)
Rifampicin	0.65 (95% CI 0.46-0.80)	0.62 (95% CI 0.51-0.72)	0.82 (95% CI 0.38-0.97)	0.62 (95% CI 0.51-0.72)
Ethambutol	0.36 (95% CI 0.03-0.90)	0.27 (95% CI 0.18-0.38)	0.33 (95% CI 0.16-0.54)	0.27 (95% CI 0.18-0.38)
Pyrazinamide	0.04 (95% CI 0.00-0.40)	0.16 (95% CI 0.10-0.26)	0.18 (95% CI 0.01-0.87)	0.16 (95% CI 0.10-0.26)

Table 3: Pooled proportions of subjects with low C_{2h} by dosing, demographic and medical covariates

Parameter	Isoniazid	Rifampicin	Ethambutol	Pyrazinamide
Per kg dosing	0.31 (95% CI 0.19-0.46)	0.70 (95% CI 0.58-0.80)	0.28 (95% CI 0.15-0.46)	0.07 (95% CI 0.03-0.15)

Standard dosing	0.51 (95% CI 0.41–0.61)	0.69 (95% CI 0.49–0.85)	0.31 95% CI (0.18–0.47)	0.12 (95% CI 0.05–0.27)
Standard combination tablets	0.88 (95% CI 0.82–0.92)	0.49 (95% CI 0.42–0.85)	0.12 (95% CI 0.05–0.24)	0.39 (95% CI 0.32–0.47)
High TB incidence	0.40 (95% CI 0.23–0.59)	0.68 (95% CI 0.58–0.76)	0.22 (95% CI 0.14–0.33)	0.12 (95% CI 0.06–0.22)
Weight > 60kg	0.41 (95% CI 0.11–0.62)	0.89 (95% CI 0.30–0.99)	0.21 (95% CI 0.07–0.50)	0.50 (95% CI 0.26–0.74)
Age > 35 years	0.42 (95% CI 0.29–0.56)	0.68 (95% CI 0.59–0.77)	0.08 (95% CI 0.01–0.43)	0.09 (95% CI 0.01–0.45)

Lei Q. et al. conducted a case-control study to analyse the relationship between two-hour serum levels of first-line anti-TB drugs and the correlative factors, as well as to establish the preliminary relevance of the outcomes. The study involved 717 patients who were admitted to Xi'an Chest Hospital from 1 August to 31 December 2018. The inclusion criteria of the patients were hospitalised and received anti-TB for at least two months and the serum anti-TB drug level concentration was measured for at least one week during hospitalisation. The regimens and number of patients received them were as shown in Table 4. During hospitalisation, the enrolled patients received the following daily doses; 300 mg INH, 450 mg RMP if the weight < 55 kg and 600 mg if heavier, 25mg/kg PZA and 15mg/kg EMB (Table 5). All of the products were single products to avoid poor absorption. The anti-TB serum level was measured with high performance liquid chromatography (HPLC). The venous blood was collected two-hours after oral drug ingestion. The expected reference ranges for each first-line anti-TB drug were recorded in Table 5. Sputum culture data was collected at the time of admission, after one month (Group Month-1) and two months (Group Month-2) in hospital. Culture conversion of Group Month-1 included patients who were initially positive but tested negative after one month and Group Month-2 included patients who were positive in the initial and after one month, but tested negative in the second month's test or more month. Among 717 patients, 17.3% were tobacco smokers and 8.4% had a history of TB. Low serum concentrations for all four anti-TB drugs were observed in numbers of patients as shown in Table 5. Based on sputum culture findings, among 717 patients; the mycobacterium TB culture data of 35 patients was missed due to specimen collection problems, the sputum culture of 360 patients were consistently negative during the treatment, the sputum culture of 208 patients in Group Month-1 were negative in one month, the sputum culture of 114 patients in Group Month-2 turned negative in two-months or more. The authors also found that the concentration of INH ($P < 0.001$), PZA ($P = 0.32$) and EMB ($P = 0.004$) was lower in the Group Month-2 compared to Group Month-1. As for individual anti-TB drugs, the concentration of two-hours INH was significantly lower among smokers than non-smokers (3.0 ug/mL versus 3.5 ug/mL; $P<0.001$). The INH concentration was also significantly higher in patients with TB history than those with initial TB (3.9 ug/mL versus 3.4 ug/mL; $P = 0.016$). Besides that, each INH dose enhancement of 1mg/kg was associated with a two-hours INH

concentration increase of 0.249 g/mL (P < 0.001). As for RMP, the analysis showed that 1 mg/kg increase of RMP for each dose was associated with a two-hours RMP concentration increase of 0.270 ug/mL (P<0.001). The concentration level of RMP was found to be higher in females compared to males (P = 0.004). Serum concentration of PZA was significantly increased with every 1mg/kg dose increment; P < 0.001 and higher serum concentration levels in females compared to males (P = 0.025). The serum concentration levels of EMB also increased with an increment of every 1mg/kg dose which was 0.145 ug/mL; P = 0.003. However, serum concentration of EMB significantly decline about 0.155 ug/ML with every 1mL/minute increment in creatinine clearance (Ccr); P = 0.002.[9, level II-2]

Table 4: First-line anti-TB regimens

Phase	Regime	Number of patients
Intensive phase	INH/RMP/PZA/EMB	495
Consolidation phase	INH/RMP	41
Intensive phase (TB patients with negative sputum)	INH/RMP/PZA	89
Consolidation phase (Relapse patients with positive sputum culture)	INH/RMP/EMB	92

Table 5: Low serum concentrations

First-line Anti-TB drugs	Dose	Numbers of patients with low serum concentrations	Reference range (ug/mL)
Isoniazid	300 mg daily	47.7% (n = 342/717)	3 to 6ug/mL
Rifampicin	600 mg daily	36.1% (n = 222/615)	8 to 24ug/mL
Pyrazinamide	Weight-adjusted daily dose of 25mg/kg	34.0% (n = 147/432)	20 to 60ug/mL
Ethambutol	Weight-adjusted daily dose of 25mg/kg	45.5% (n = 204/448)	2 to 6µg/mL

Park JS et al. conducted a retrospective cohort study to evaluate the prevalence of low drug levels and the clinical impact of serum levels of first-line anti-TB drugs during TB treatment. The study involved data from 413 patients that were diagnosed with TB in Seoul National University Bundang Hospital, Korea. All the patients had received daily anti-TB drugs at least one week before the measurement of serum anti-TB drug levels. Fifteen-point seven percent (15.7%) of patients had a previous history of TB treatment. The serum levels were measured 2-hour after drug ingestion with HPLC/tandem mass spectrometry. The dose of anti-TB drugs for each patient and the therapeutic level for each drug were tabulated in Table 6. The patients were followed-up for two-years after the TB treatment was completed. The treatment was successful if the patients were cured (negative sputum culture in the last month and on ≥

one previous) and completed the treatment (completed the anti-TB treatment but did not meet the criteria of cure or failure). Meanwhile, the treatment failed if the sputum smear or culture was positive at 5 months or later during treatment. Drug susceptibility test (DST) was performed in 243 (58.8%) patients. There were 36 patients resistant to at least one of the anti-TB drugs and nine of them presented with initial MDR-TB. Prevalence of low serum concentrations were detected and the findings were shown in Table 6. According to the authors, patients with low INH levels were more common among patients who were previously treated with anti-TB drugs. In addition, low INH patients had more drug-resistant strains than normal INH groups (17.6% versus 8.8%; P = 0.049). Besides that, the authors reported that the signs of severe disease in chest radiographs were more frequent in the low INH group than in the normal INH group. The authors also observed the recurrence rate. They found that either two-month culture rate, treatment outcomes and recurrence rates were not significantly different between the low and normal drug levels. Among 413 patients, 17 (4.1%) patients experience recurrence and 13 of them initially showed low levels of INH. Among the recurrence patient, two patients presented with MDR-TB and another two were with INH-resistant TB. The authors also observed the risk factors related to low INH levels. They found that male sex, high acetyl INH/INH ratio and low INH dose per kg of body weight were independent risk factors of INH levels. Although low level INH had a tendency to be associated with two-month culture positivity, the association was not statistically significant (P = 0.072). The authors finally concluded that they could not really determine whether low INH level was directly related to treatment response of recurrence rate. The role and routine TDM for general TB patients require further evaluation in prospective study.[10, level II-1]

Table 6: Dose of Anti-TB Drugs, Therapeutic Levels / Prevalence of Low Serum Concentrations

Anti-Tuberculosis Drugs (First-line)	Dose of Anti-Tuberculosis Drugs		Therapeutic levels	Prevalence of low serum concentration
	For <50 kg patients	For >50 kg patients		
Isoniazid	300mg	300mg to 400mg	3 - 6µg/mL	245 out of 409 patients (59.3%)
Rifampicin	450mg	600mg	8 - 24 µg/mL	115 out of 413 patients (27.8%)
Ethambutol	600mg	800mg	2 - 6 µg/mL	53 out of 413 patients (12.8%)
Pyrazinamide	1000mg	1500mg	20-50 µg/mL	33 out of 378 patients (8.0%) *

*Number of patients received PZA lower than other anti-TB drugs because some patients stopped PZA due to adverse drugs events (ADR)

Prahl JB. conducted a prospective cohort to determine the relationship between two-hour plasma concentrations of the first-line tuberculosis drugs and clinical outcome in a cohort of patients with TB in Denmark. The study period was within 1 January 2009 to 31 March 2011 with one-year follow-up to review the clinical files at hospitals and lab records. The study involved 35 TB patients which were divided into Group A (10 patients from inpatient and

outpatient clinics in the eastern part of Denmark and underwent TDM for clinical reasons) and Group B (consisted of 25 consecutive inpatients and outpatients identified at Department of Infectious Diseases at university hospitals. Light chromatography tandem mass-spectrometry was used and the venous blood samples were collected two-hour after ingestion of the anti-TB medication. The duration of treatment at the time of sampling ranged between six and 207 days. The number of patients who received each drug and the median plasma concentrations of the TB drugs after two-hour were tabulated in Table 7. Of the 35 patients included, 86% (30/35) had plasma concentration of at least one drug below the normal range. The findings for those drugs were also shown in Table 7. At one-year follow-up after treatment, three patients with active TB were transferred out and the original isolate from one patient was found to be resistant to isoniazid, so the follow-up was only possible for 28 patients. Five patients failed treatment where three of them died during treatment and two patients experienced relapse of TB within one year after the end of the therapy. The authors reported that patients with subsequent therapy failure more often had excessive alcohol and higher C-reactive protein (CRP) levels, however the relationship was not significant; median CRP 87 versus 42mg/L, P = 0.089) compared with successful outcome. On the other hand, the median number of days on treatment at the time of sampling was 34 days for patients experiencing therapy failure versus 61 days for patients with successful outcome (P = 0.928). Patients with therapy failure attained significantly lower plasma concentrations of INH than successful treatment despite the fact that they received a higher dosage of INH per kg body weight. When dividing the patients into two groups on the normal values suggested in literature, it was observed that significantly more patients with both low RMP and INH concentrations experienced therapy failure (5/13 versus 0/15, P = 0.013). In addition, therapy failure was observed more frequently in patients with below median values of RMP (5/15 versus 0/13, P = 0.044), of INH (5/14 versus 0/14, P = 0.0041) and both drugs (5/11 versus 0/17, P = 0.005). In univariate logistic regression analysis, therapy failure was inversely associated with the plasma concentration of isoniazid (P = 0.021) and with the CRP level at baseline (P= 0.056).[11, level II-3]

Table 7: Normal range and after two-hour plasma concentration (C_{2h})

First-line TB drug	Validation value for LC-MS/MS)		Median plasma concentration	Number of patients below normal range (86% [30/35])
	Normal range	Lower limit		
Isoniazid	0.5 – 10mg/L	0.5mg/L	2.1mg/L (Range 0.5 – 12.1mg/L)	71% (25/35)
Rifampicin	0.75 – 30mg/L	0.75mg/L	6.5mg/L (Range 0 - 31.0mg/L)	58% (19/33)
Ethambutol	0.25-10mg/L	0.25mg/L	2.2mg/L (Range 0.5 – 5.9mg/L)	46% (13/28)
Pyrazinamide	4 – 80mg/L	4.0mg/L	31.3mg/L	10% (3/29)

			(Range 14.9 – 10.2mg/L)	

Lee SH et al. conducted a retrospective cohort to determine the frequencies of low serum concentrations of anti-MDR-TB drugs and to analyse the effects of the drugs concentrations on two-month sputum conversion in MDR-TB patients. The second-line TB treatments involved were moxifloxacin (MF), prothionamide (PTH) and cycloserine (CS). The doses of those drugs and number of patients received were shown in Table 8. The study was retrospectively analysed by Inje University Busan Paik Hospital, Korea and included patients 18 to 75 years of age who were MDR-TB. Those patients were at least resistant to INH and RMP based on in-vitro DST. The venous blood was drawn two - six hour after the drug ingested during the patient's monthly visit. The number of samples per drug collected between second- and three-hours post-dose. The references in serum levels of the second-line anti-TB were stated in Table 8. The serum concentrations were measured with high-pressure liquid chromatography-tandem mass spectrometry (HPLC). For HPLC, the validation of the assays performed according to the USFDA guidance and calibration curves were established for each drug. The sputum AFB culture conversion was defined as two or more consecutive negative sputum cultures tested at least four weeks apart. The median serum levels for each drug in the two-month sputum conversion group and two-month sputum non-conversion group were compared. The results were divided based on sputum conversion and were gathered in Table 9. After two-month of treatment, four patients experienced sputum non-converted and another 25 patients were sputum-converted. However, there were no significant differences in clinical characteristics except drug compliance between the converted group and non-converted group. The frequency of low serum MF concentrations below the minimal range was 83.3% (20/24). In the conversion group the frequency of low serum MF was 85.0% (17/20) compared with 75% (3 / 4) in the non-conversion group, but not statistically significant. For PTH, the frequency of serum PTH concentrations below the minimal range was 59.2% (29/49) where the concentrations below minimal normal range was 57.8% (26/45) in the conversion group and 75% (3 / 4) in the non-conversion group, but not statistically significant. As for CS, total frequency of serum concentrations below the minimal range was 71.2% (47/66); 70.5% (43/61) in conversion group and 80% (4 / 5) in the non-conversion group which was also not significant. The medium serum concentrations in two-month sputum in both groups were in Table 9. Differences in sputum conversion after two-months of treatment showed that the number of TB drugs used during the initial two-months of therapy did not differ between sputum Conversion Group (5.0 ± 0.6) and non-Conversion group (5.8 ± 1.0). The number of patients with previous TB history (60% [15/25] versus 25% [1 / 4]; p = 0.299) and the number of resistant TB drugs on drug sensitivity test per patient was not significantly different between the two groups (3.0 drugs, IQR 2.5-4.5 versus 6.0 drugs IQR 3.3-8.8).[12, level II-2]

Table 8: Dosing and reference level of second-line TB treatment

Second-line anti-TB	Dose	Number of patients received	Reference level (Serum) [ug/mL]	
			Normal level	Low level
Moxifloxacin	400mg PO daily	29	2.3 - 4.5	< 2.5 (400mg PO daily dose)
Prothionamide	250mg PO BD (for btw < 50kg) 500mg (for bwt ≥ 50kg) BD	34	1 - 5	< 1 (500 - 100mg PO daily dose)
Cycloserine	250mg PO BD (for bwt < 50kg) 500mg PO BD (for bwt ≥ 50kg)	15 (bwt < 50kg) 17 (bwt > 50kg)	20 - 35	< 20 (500 - 1000mg PO daily dose)

Table 9: Result for median serum concentration in Conversion and Non-Conversion Group

Anti-TB	Groups	Parameter	
		Frequency of low serum concentration	p-value
Moxifloxacin	2-month Conversion group (n = 25)	1.46 (95% CI 0.33 - 2.17)	0.394
	2-months Non-conversion Group (n = 4)	1.60 (95% CI 0.93 - 2.54)	
Prothionamide	2-month Conversion group (n = 25)	0.93 (95% CI 0.35 - 2.34)	0.597
	2-months Non-conversion Group (n = 4)	0.70 (95% CI 0.24 - 1.28)	
Cycloserine	2-month Conversion group (n = 25)	15.10 (95% CI 8.23 - 21.65)	0.981
	2-months Non-conversion Group (n = 4)	14.90 (95% CI 9.89 - 19.45)	

Mukherjee A. et al. conducted a case-control study to describe the influence of HIV infection on PK of INH, RMP, PZA and EMB in children. The study was conducted in All India Institute of Medical Sciences (AIIMS), India from October 2009 to September 2013. There were 24 HIV-TB co-infected and 32 non-HIV TB children involved in this study. The patients were children aged six months to 15-years old and were newly diagnosed with TB either pulmonary or extrapulmonary. The TB treatment was four first-line drugs (INH, RMP, PZA and EMB) for the first two–months followed by two drugs (INH and RMP) during four months of maintenance phase. Antiretroviral therapy (ART) was initiated for all HIV positive patients; Efavirenz (EFV) based regimen was prescribed for all cases except for those below three-years old or less than 10kg body weight in which case Nevirapine (NVP) was prescribed. Blood samples were collected 14 days (up to 30 days) after starting the TB treatment. The level of the anti-TB drugs was measured with liquid chromatography-mass spectrometry. All

the children were follow-up every month until completed the anti-TB treatment followed by every three months for six months thereafter. Any changes or extension of anti-TB regimens and death was considered treatment failure. The pharmacokinetic (PK) parameters for the maximum plasma concentration (C_{max}) achieved and the time taken to achieve maximum concentration (T_{max}) were determined by visual inspection of the data. The AUC from zero to four-hour (AUC_{0-4}) was calculated by the linear trapezoidal rule. Based on the analysis, the 2-hour GMC (C_{max}), AUC_{0-4} and T_{max} of both the HIV and non-HIV groups were similar for INH, RMP and PZA. The results were shown in Table 10. All (100%) the HIV-TB co-infected children were fast acetylators, meanwhile 25 (80.6%) of the non-HIV patients were fast acetylators. For EMB, the median EMB concentrations were significantly lower in HIV-infected children at all measured time points than in non-HIV children. The mean AUC_{0-4} for EMB was lower and the T_{max} shorter in children with HIV-TB, meanwhile the C_{max} was similar in both groups. When children on ART were compared with non-HIV children; C_{2h} of EMB were significantly lower in children on ART (GMC 0.38µg/mL, 95% CI 0.23-0.63 versus 0.81µg/mL, 95% CI 0.57-1.15, P = 0.01). Table 10 also showed that a large proportion of children in both groups had low 2-hour levels of INH, RMP and EMB. The PZA level was adequate in children. When multivariable analysis was conducted to look at the association factors with low levels of INH, the analysis showed that younger age (P = 0.04) and lower dose of INH in mg/kg (P = 0.01) were significantly associated with a lower 2-hour INH concentration. The authors also observed the plasma concentration of EFV and RMP where the median plasma EFV concentration was estimated in 16 children with HIV-TB was 3.57µg/mL (IQR 1.64 – 5.15). Ten children (62.5%) had plasma EFV levels within the therapeutic range of 1 - 4µg/mL. Only one child had a plasma concentration less than 1µg/mL. The correlation coefficient between the C_{max} of RMP and EFV concentration was 0.04 (P = 0.89). The C_{max} and AUC_{0-4} of RMP were similar, irrespective of whether or not the children received EFV. The T_{max} for RMP tended to be longer in children who received EFV (2-hour versus 1-hour, P = 0.09). The treatment outcome data available in 23 children with HIV-TB at the end of 6-months of anti-TB treatment; out of 23 children, 17 (73.9%) had treatment failure. No association observed between INH, RMP, PZA and EMB plasma concentrations and treatment outcome (data not shown).[16, level II-2]

Table 10: Pharmacokinetic parameters of INH, RMP, PZA and EMB in HIV-Infected Children with TB[16]

Drugs	HIV status	2h concentration (ug/ml) GM (95% CI)	C_{max} (ug/ml) GM (95% CI)	AUC_{0-4} (ug/ml*h) GM (95% CI)	Tmax h, mean ± SD	Children with low 2h concentrations*	
						n (%)	95% CI
INH	HIV+	0.62 (0.43-0.89)	0.99 (0.73-1.34)	2.04 (1.53-2.74)	1.3±0.7	22 (91.7)	74.1-97.7
	HIV-	0.41 (0.24-0.68)	0.58 (0.35-0.97)	1.31 (0.77-2.22)	1.7±1.1	29 (90.6)	75.0-97.5
RMP**	HIV+	4.39 (0.51-7.72)	7.76 (5.61-10.73)	18.47 (13.29-25.67)	1.9±1.03	12 (50)	31.9-55.9
	HIV-	6.05 (3.97-9.23)	9.15 (6.69-12.51)	22.62 (16.68-30.35)	1.8±1.1	13 (40.6)	25.5-57.8
PZA	HIV+	45.58	55.13	143.66	1.6±0.9	1 (4.2)	0.7-20.2

		(35.61-58.33)	(47.57-63.89)	(120.47-171.32)			
	HIV-	46.02 (37.78-56.07)	54.46 (45.12-65.71)	159.03 (132.17-191.36)	1.9±1.2	2 (6.2)	0.7-21.2
EMB***	HIV+	0.43# (0.27-0.69)	0.80 (0.53-1.19)	1.55# (1.06-2.25)	2.3±1.2	21 (87.5)	69.0-95.7
	HIV-	0.81 (0.57-1.15)	1.13 (0.74-1.74)	2.79# (2.02-3.87)	1.5±0.9	24 (75.0)	57.7-86.9

*Low 2h plasma concentrations: INH <3ug/ml, RMP <8ug/ml, PZA <20ug/ml, EMB <2ug/ml at 2h post-drug time point

**Very low 2h RMP concentration (<4ug/ml) was found in respectively 8 (33.3%, 95% CI 17.9-53.3) and 6 (18.7%, 95% CI 8.5-35.7) HIV co-infected and non-HIV-infected children with TB

***Very low 2 h EMB concentration (,1 lg/ml) was found in respectively 19 (79.17%, 95%CI 59.5–90.8) and 21 (65.6%, 95%CI: 48.2–79.7) children suffering from TB, with or without HIV

#P<0.05; other comparisons are non-significant

5.1.2 Therapeutic Drug Monitoring and Dose Adjustment

Heysell SK et. al. conducted a retrospective cohort to describe TDM usage patterns and PK for patients treated for MDR-TB in Virginia from 2009 – 2014 and relate these findings to emerging trends in TB management. Data of state TB of all patients with *Mycobacterium tuberculosis* and microbiologically confirmed resistance to INH and RMP from 2009 – 2014 was searched. The additional drug resistance results by conventional phenotypic drug-susceptibility testing (DST) were performed per routine at the state TB laboratory for first line TB-drugs (INH, RMP, Streptomycin, PMZ and EMB) and second-line TB-drugs (cycloserine, capreomycin, linezolid and moxifloxacin) at more than one referral lab. The TDM used was validated HPLC, gas chromatography-mass spectrometry and colorimetric assays. However, the study involved only six males and four female patients. The TDM was performed in eight patients for at least one drug, meanwhile another two patients without TDM (one patient died at early phase and another patient was transferred out of care). The initial TDM was performed at a median of 6.5 weeks (minimum of 2 weeks and maximum of 14 weeks) after MDR-TB treatment initiation. Out of the eight patients, six had at least one follow-up concentration with TDM. Out of eight patients, cycloserine was the most common medication for TDM and was tested in seven patients. The cycloserine values were below the expected range in four (57%) of initial concentrations (mean 16.6 ± 10.2µg/mL). As for moxifloxacin that was used in patients with fluoroquinolone-susceptible MDR-TB at 400mg daily, with TDM, the initial C_{2h} value was below the expected range (mean 3.2 ± 1.5µg/mL). One patient with low initial C_{2h} (0.68µg/mL) of moxifloxacin had increased the dose up to 600mg daily and the C_{2h} were increased within the expected range (4.7µg/mL). Another second-line TB-drugs were capreomycin, the most commonly used injectable TB-drugs. The TDM showed that capreomycin concentration was below the expected peak range in three (60%) patients with mean value of 21.5µg/mL ± 14.0µg/mL. The six-hour concentration (C_{6h}) of capreomycin were measured, and the peak concentration was also below the expected range. Another anti-TB drug was linezolid that was used in three patients with pre-XDR-TB. The initial C_{2h} values were within the expected range in patients who received 600mg daily dose but low in patients who received 400mg daily dose. The treatment outcomes showed that seven patients were either cured or clinically improved and one patient was transferred back to home country within one month of treatment and the outcome was unknown. The TDM

results for all seven patients were within the normal range. The authors recommended a more formalised approach to TDM in the management of MDR-TB including routine use as early as possible after a tolerable regimen was established. Follow-up TDM without dose adjustment was unnecessary and may only add expense.[14, level II-2]

Hung WY et al. conducted another cohort to investigate serum cycloserine concentration among MDR-TB patients. The study involved 32 patients consisting of 23 men and nine women at mean age of 42.9 ± 17.1 years. The study was conducted at Taipei Medical University (Wan Fang Hospital). The venous blood was obtained two-hour after CS administration for measurement of peak serum concentrations and at six-hour to evaluate delayed absorption. The measurement was taken with the HPLC-tandem mass spectrometer. The patients were on CS for at least five days. The daily dosage of CS was targeted around 10mg/kg but was reduced to 250mg daily in patients with severe renal impairment. Patients were administered CS once, twice or three times daily designated dosages of 250mg, 500mg or 750mg per day. Most of the patients received daily divided dosage of CS of 500mg/day with mean daily dosage of 8.8 ± 1.3mg/kg body weight. Cured patients were defined as patients who had at least five consecutive negative cultures taken at least 30 days apart during the final 12 months of treatment. Meanwhile, sputum conversion was two sets of consecutive negative smears and cultures taken 30 days apart. The results showed that mean serum concentration at two-hour after drug administration was 19.7 ± 8.3ug/ml (range 7.1 - 43.4), meanwhile at six-hour was 18.1 ± 8.7ug/ml (range - 42.6). Most of the patients had serum concentration of between 10 and 30ug/ml. From the findings, the authors found that seven patients (22%) had serum concentration at two-hour lower than the dose at six-hour, suggesting delayed absorption. Out of 32 patients, 12 (38%) patients had their highest drug serum concentrations between 20 and 35ug/ml while 18 patients (56%) had both two-hour and six-hour concentrations <20ug/ml. Another two patients (6%) had >35ug/ml. In order to correlate the CS dosages and serum concentrations, they found significant correlations between peak concentrations and doses in all patients ($R = 0.49$, $P = 0.008$) and in GFR 60ml/min/1.73m2 group ($R = 0.53$, $P = 0.009$) but not significant for GFR >90ml/min/1.73m2 group ($R = 0.30$, $P = 0.09$). At the end of December 2011, all the 12 patients with peak serum concentration of between 20 and 35ug/ml were cured. Among 18 patients with both two- and six-hour concentrations less than 20ug/ml, 17 patients were cured and one patient died after sputum conversion; however, the death was not related to TB. From the findings, delayed absorption and lower than recommended serum CS concentrations were frequent in the MDR-TB involved in the study, thus clinically feasible TDM might be possible to maintain CS concentrations within the recommended range.[15, level II-2]

Pea F. et al. conducted a case-control study to define possibly useful pharmacodynamic (PDD) thresholds to improve safety outcomes of linezolid by assessing the relationship between linezolid exposure over time and outcomes in adult patients who underwent long-term treatment with linezolid. The study was carried out between March 2004 and December

2010 at Azienda Ospedaliero Universitaria Santa Maria della Misericordia, Italy. The 45 included participants were outpatients (>18-years old) who were treated with linezolid more than 28 days (prolonged). The patients were divided into two-subgroups; 35 patients in the linezolid alone group (Linezolid group) and 10 patients in the linezolid with the rifampicin group (Linezolid-RMP group). The venous blood samples were collected just prior to the next administration to assess trough plasma concentration (C_{min}) and two-hour after oral administration to assess the peak plasma concentration (C_{max}). The plasma concentration was measured with validated HPLC analysis and the precision and accuracy were assessed by performing replicate analyses of quality control samples against calibration standard, intra- and inter-assay coefficients of variation always being <10%. Patients were defined as recovered if there was no clinical, biological and/ or radiological evidence of infection at the end of treatment and as cured if the status was confirmed at one-year follow-up. Meanwhile, failure was defined as any discontinuation of linezolid before the end of treatment, either because of toxicity or due to persistence of infection. The median instances of TDM were seven in Linezolid group and five in Linezolid-RMP group. The study reported that dosage adjustments over time to avoid potential linezolid overexposure were needed in 40% of patients in Linezolid group (14 of 35 patients) and none adjustment required in Linezolid-RMP group. Although similar total daily doses of linezolid were used in both groups, those patients who received linezolid alone had significantly higher C_{min} (3.71mg/L [1.43 - 6.38] versus 1.37mg/L [0.67 - 2.55], P < 0.001) or AUC_{24} (212.77mg/L.h [166.67 - 278.42] versus 123.33mg/L.h [97.36 - 187.94], P<0.001) than those in Linezolid-RMP group. There were 41.4% of cases with C_{min} <1 mg/L in the Linezolid group. In terms of drug exposure, it remained significantly different between the two groups even after dosage normalisation for body weight (median C_{min} [IQR] per each mg/kg/day of linezolid was 259.7 [124.2 - 488.4] versus 85.8 [37.5 - 180.6] ug/L, P < 0.001). The authors also found that co-treatments with omeprazole were more frequent in the Linezolid group than Linezolid-RMP group (34.2% versus 0%, P = 0.042). As for recovery rates, both groups showed high recovery rates; 76.5% after a median length of treatment of 63 days in Linezolid group and 60% after a median length of treatment of 77 days in Linezolid-RMP groups, P = 0.422. However, failure due to persistence of infection was observed in three patients in Linezolid-RMP groups after a median length of treatment of 21.5 days (IQR 16 - 29 days) and only one in Linezolid group. Based on the findings, TDM-guided dosage adjustments necessary in patients co-treated with other drugs or in those who presented with peculiar pathophysiological conditions.[16, level II-2]

5.2 SAFETY

There was no safety issue related to TDM towards TB patients. As for safety monitoring, TDM used for assessing patient's safety regarding any anti-TB toxicity related to overexposure or irresponsive patients towards anti-TB treatment due to low dose concentration.

Heysell SK et. al. reported one death in patients with below expected concentration range of capreomycin and linezolid near the time of death. However, the cause of death was uncertain and possibly TB-related.[14]

Lee SH et. al. reported in their study that second-line anti-TB drug toxicity rates were not significantly different between sputum Conversion Group and Non-Conversion Group 98% [2/25] versus 50% [2/4]; p = 0.080).[12]

Hung WY et. al. reported that, only one patient experienced a major adverse drug effect associated with CS. Despite an estimated GFR of 120ml/min/1.73m2 and a reasonable dose of 12.4 mg/kg, both two- and six-hour serum concentrations were >35 ug/mL and the patient developed psychotic symptoms, including persecutory delusion and aggressiveness, for which the Naranjo score was 5, indicating probable causality. Serum concentration was measured during the period of symptoms. The adverse effects subsided soon after the dosage had been reduced from 500 mg to 250 mg/day.[15]

Pea F. et. al. found out that two patients in the Linezolid Group experienced thrombocytopaenia due to linezolid overexposure. The TDM was conducted to guide dosage reductions with normalization of plasma concentrations and progressive recovery from toxicity, which allowed for the continuation of therapy until the planned end of treatment with good clinical outcome. Discontinuation of therapy due to severe thrombocytopenia was necessary in five patients of the Linezolid Group. According to the logistic regression model, there were strong significant correlations between the probability of thrombocytopaenia and either linezolid C_{min} (r2=0.75) or linezolid AUC_{24} (r2=0.79). The estimated probability of thrombocytopaenia was 50% in the presence of C_{min} 6.53 mg/L and/or AUC_{24} 280.74 g/L.h and rose to values >95% in the presence of C_{min} 9.96 mg/L and AUC_{24} or 343.02 mg/L.h.[16]

Cojutti P. et. al. conducted a retrospective cohort to explore the relationship between isoniazid plasma exposure and the risk of developing hepatotoxicity the study was conducted between January 2005 and December 2012 among all adult's patients who were admitted with a diagnosis of TB to Clinic of Infectious Disease of the Azienda Ospedalierro-Universitaria of Udine and underwent assessment of isoniazid plasma exposure. A total of 185 patients were included in the study and data on isoniazid plasma pharmacokinetics and data on alanine transferase (ALT) trend over time (at baseline and at days 7, 14, 30, 60, 90, 120, 150 and 180 from the start of therapy) were collected. The hepatotoxicity was defined as an elevation of ALT over the upper limit of normal (ULN ≥51 IU/L) occurring at any time during isoniazid treatment. The plasma exposure to isoniazid; AUC_{24} during a dosing interval (blood sampling times: 0, 0.5, 1, 2, 3 ,5 9, 12 and 24-hour after dosing) was routinely assessed in all the patients. In the study, the authors observed that hepatotoxicity occurred in 22.2% of patients (41/185) and the patients had the isoniazid AUC_{24} values significantly higher than among those who did not (58.33 ± 18.59 versus 31.28 ± 13.96 mg.h/L, p<0.001). Dose adjustment was conducted in 63.41% (26/41) patients and the ALT level was normalized in 23 patients out of 26 patients. The authors conducted further analysis, from logistic regression analysis they found that the likelihood of developing hepatotoxicity was 50% for an isoniazid AUC_{24} of 53.7 mg.h/L and reached 90% for an AUC_{24} of 70.0 mg.h/L. Another analysis, Kaplan-Meier analysis of hepatotoxicity, they found that almost all patients who developed hepatotoxicity (38/41, 93%) experienced it within one month after starting the treatment.[17]

5.3 ORGANISATIONAL ISSUES

Lee SH et. al. reported that the poor compliance rate was significantly greater in the two-month sputum Non-Conversion Group (75.0%, 3 / 4) than in the two-month sputum Conversion Group (0%, 025; p = 0.001).[12]

5.4 ECONOMIC IMPLICATION

There was no retrievable study on economic evaluation of TDM in tuberculosis treatment.

5.5 LIMITATIONS

Author acknowledge some limitations in the review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited the study numbers. Most of the included studies were mainly on the level of therapeutic concentrations of anti-TB detected by TDM process; only a few studies that specifically look at the function of TDM either in the effectiveness, toxic or below therapeutic level of anti-TB. On the other hand, some studies involved a small number of patients which might not reflect the desired outcome.

6.0 CONCLUSION

Efficacy/Effectiveness

In patients on first line anti-TB treatment, concentration level of the anti-TB drugs was not associated with patient outcome. However, for second line anti-TB drugs, TDM was used to ensure therapeutic drug level to avoid toxicity.

Safety

No evidence retrieved regarding the safety of TDM used in anti-TB drugs. However, TDM used for detection of any over dosage or low dose anti-tuberculosis among patients with sign and symptom of toxicity and unresponsive towards treatment.

Organisational

Poor compliance of anti-TB drug was reported in sputum non-conversion group compared to sputum conversion group.

Economic implication

No cost-effectiveness study retrieved related to TDM for anti-TB drug

7.0 REFERENCES

1. Goroh MMD, Rajahram GS, Avoi R et al. Epidemiology of Tuberculosis in Sabah, Malaysia, 2012-2018. Infect Dis Poverty. 2020; 9: 119
2. Global Tuberculosis Report 2020. Available at: https://www.who.int/teams/global-tuberculosis-programme/tb-reports
3. Mota L, Al-Efraij K, Campbell JR, Cook VJ, Marra F. & Johnston J. Therapeutic drug monitoring in anti-tuberculosis treatment: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2016; 20(6): 819-826.
4. Kang JS and Lee MH. Overview of Therapeutic Drug Monitoring. Korean J Intern Med 2009;24:1-10
5. MS Bolhuis et al. Individualized treatment of multidrug-resistant tuberculosis using therapeutic drug monitoring. Int. J. Mycobacteriol. (2016), http://dx.doi.org/10.1016/j.ijmyco.2016.07.003
6. Prashanth P, Patil N, Reddy SK, et. al. Therapeutic Drug Monitoring and HPLC: A Review. Pharmacologyonline. 2011; 3: 1176-1191
7. Alffenaar J-WillemC, Akkerman OW, Kim HY, Tiberi S, Battista Migliori G, Precision and Personalized Medicine and anti–TB treatment: Is TDM feasible for programmatic use? International Journal of Infectious Diseases (2020). doi: https://doi.org/10.1016/j.ijid.2020.01.041
8. Management of Tuberculosis, CPG Guideline, Ministry of Health Malaysia, 2012
9. Lei Q, Wang H, Zhao Y, Dang L, Zhu C et al. Determinants of Serum Concentration of First-line Anti-TB Drugs from China. Medicine. 2019 Oct;98(41):e17523
10. Park JS, Lee JY, Lee YJ, Kim SJ, Cho YJ, Yoon HI, Lee CT, Song J & Lee JH. Serum Levels of Anti-Tuberculosis Drugs and Their Effect on Tuberculosis Treatment Outcome. Antimicrob. Agents Chemother. 2015
11. Prahl JB, Johansen IS, Cohen AS, Frimodt-Moller N & Andersen AB. Clinical Significance of 2 h Plasma Concentrations of First-Line Anti-Tuberculosis Drugs: A Prospective Observational Study. J Antimicrob Chemother. 2014; 69(10):2841-7
12. Lee SH, Seo KH, Lee YM, Lee HK, Kim JH, Shin C, Ghim JR, Shin JG & Kim DH. Low serum concentrations of Moxifloxacin, Prothionamide and Cycloserine on sputum conversion in Multi-Drug Resistant TB. Yonsei Med J. 2015; 56(4): 961-967

13. Mukherjee A, Velpandian T, Singla M, Kanhiya K. et al. Pharmacokinetics of isoniazid, rifampicin, pyrazinamide and ethambutol in HIV-infected Indian children. Int. J. Tuberc. Lung Dis. 2016; 20(5): 666-672
14. Heysell SK, Moore JL, Peloquin CA, Ashkin D & Houpt ER. Outcomes and use of therapeutic drug monitoring in Multidrug-Resistant Tuberculosis (MDRTB) Patients Treated in Virginia, 2009-2014. Tuberc Respir Dis 2015; 78:78-84.
15. Hung WY, Yu MC, Ching YC, Chang JH, Chiang CY, Chang CC, Chuang HC & Bai KJ. Serum concentrations of cycloserine and outcome of MDR-TB in Northern Taiwan. Int J Tuberc Lung Dis. 2014; 18 (5): 601-606
16. Pea F, Viale P, Cojutti P, Pin BD, Zamparini E & Furlanut M. Therapeutic Drug Monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012; 67: 2034-2042
17. Cojutti P, Duranti S, Isola M et. al. Might isoniazid plasma exposure be a valuable predictor of drug-related hepatotoxicity risk among adult patients with TB? J Antimicrob Chemother. 2016; 71: 1323-1329

8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVID MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 10th August 2021

1.Tuberculosis/
2. tuberculos#s.tw.
3. (mycobacterium tuberculos#s adj1 infection$).tw.
4. koch$ disease$.tw.
5. koch's disease$.tw.
6. 1 or 2 or 3 or 4 or 5
7. 1 or 2 or 3 or 4 or 5 or 6
8. Antitubercular Agents/
9. (Antitubercul$ adj1 agent$).tw.
10. (Anti-tubercul$ adj1 agent$).tw.
11. (Tubercul$ adj1 agent$).tw.
12. (Anti tubercul$ adj1 agent$).tw.
13. (Antitubercul$ adj1 drug$).tw.
14. (Anti-tubercul$ adj1 drug$).tw.
15. (Tubercul$ adj1 drug$).tw.
16. (Anti tubercul$ adj1 drug$).tw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. Rifampin/
19. Rifampi$.tw.
20. Benemycin.tw.
21. Rifadin.tw.
22. Rimactan$.tw.
23. Tubocin.tw.
24. vtj6j7r4tr.tw.
25. 13292-46-1.tw.
26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. Isoniazid/
28. Isoniazid.tw.
29. 149-17-7.tw.
30. 40q4c3o4v0.tw.
31. 54-85-3.tw.
32. (vanillylidenehydrazide, isonicotinic adj1 acid).tw.
33. ftivazide.tw.
34. (isonicotinic acid adj1 hydrazide).tw.
35. isonex.tw.
36.(isonicotinic acid adj1 vanillylidenehydrazide).tw.
37. phthivazid$.tw.
38. tubazide.tw.

39. v83o1voz8l.tw.
40. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. Pyrazinamide/
42. Pyrazinamide.tw.
43. 2kni5n06ti.tw.
44. 98-96-4.tw.
45. Tisamid.tw.
46. 41 or 42 or 43 or 44 or 45
47. Ethambutol/
48. ethambutol.tw.
49. (Ethambutol adj1 hydrochloride).tw.
50. 1070-11-7.tw.
51. 74-55-5.tw.
52. 8g167061qz.tw.
53. Dexambutol.tw.
54. Emb fatol.tw.
55. Emb hefa.tw.
56. Emb-fatol.tw.
57. Emb-hefa.tw.
58. (Etambutol adj1 llorente).tw.
59. Etibi.tw.
60. M#ambutol.tw.
61. Qe4vw5fo07.tw.
62. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63. Streptomycin/
64. Streptomycin$.tw.
65. 57-92-1.tw.
66. Cw25ikj202.tw.
67. (Estreptomicina adj (cepa or clariana or normon)).tw.
68. (Strepto adj (fatol or hefa)).tw.
69. Strepto-fatol.tw.
70. Strepto-hefa.tw.
71. (Streptomycin$ adj (grunenthal or sulfate or sulphate or panpharma)).tw.
72. Y45qso73ob.tw.
73. 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. Amikacin/
75. amikacin$.tw.
76. 37517-28-5.tw.
77. 84319sgc3c.tw.
78. (amikacin$ adj1 (sulfate or medical or normon)).tw.
79. amikafur.tw.
80. amikalem.tw.
81. amikasons.tw.
82. amikayect.tw.
83. am#kin.tw.
84. amiklin.tw.
85. bb k 8.tw.
86. bb k8.tw.
87. bb-k8.tw.
88. bbk 8.tw.
89. bi#lin.tw.
90. gamikal.tw.
91. kanbine.tw.
92. oprad.tw.
93. yectamid.tw.
94. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93
95. 17 or 26 or 40 or 46 or 62 or 73 or 94
96. therapeutic drug monitoring.mp. or Drug Monitoring/
97. (Drug$ adj1 monitoring).tw.
98. (Therapeutic adj1 drug$ monitoring).tw.
99. (Monitoring adj1 therapeutic drug$).tw.
100. Tdm.tw.

Other Databases		
MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE		Same MeSH, keywords, limits used as per MEDLINE search
PubMed		Same MeSH and keywords as per MEDLINE search
INAHTA		
US FDA		

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

9 EVIDENCE TABLE

(Provided upon request)

e ISBN 978-967-2887-18-8